ARTICLE

The Long-term Outcomes of Pediatric Pleural Empyema

A Prospective Study

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Objective: To describe the long-term outcomes of pediatric pleural empyema.

Design: Prospective observational study from October 2008 to October 2011.

Setting: Tertiary care children's hospital.

Participants: Children with pleural empyema (loculations and/or septations identified on radiologic imaging or frank pus on thoracentesis).

Main Outcome Measures: Children were seen 1, 6, and 12 months postdischarge. Outcome measures included symptoms and signs of respiratory disease, child and parental impact, radiographic resolution, spirometry, and health-related quality of life (Pediatric Quality of Life Inventory score). Analysis was based on the last observation carried forward for missing data.

Results: Eighty-two of 88 patients (93%) eligible were recruited. Fifty-four percent were male and mean (SD) age was 4.5 (3.4) years. Outcome data was obtained in 100% at 1 month, 90% at 6 months, and 72% at 1 year. Seventy-one percent had effusions occupying a quarter or more of the hemithorax and 62% of effusions were drained. Fever, cough, parental work loss, child school loss, radiographic abnormalities, and abnormal spirometry results were common in the first month and then declined. By the last observation, 2% of patients had abnormal radiographs (aside from pleural thickening), 6% had mild obstruction on spirometry, and Pediatric Quality of Life Inventory scores were better than for children with asthma ($P < .001$). Patients with abnormal outcomes in 1 measure had normal outcomes in all other clinical measures.

Conclusions: Clinically important phenomena persist in the short-term, but virtually all children with pleural empyema have no long-term sequelae.

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PNEUMONIA IS ONE OF THE most common reasons for hospitalization in childhood.[1] Up to 50% of children hospitalized with pneumonia have an associated parapneumonic effusion,[2] and a subset of these develop into a complicated effusion characterized by enlargement and/or extensive loculations leading to respiratory compromise. The incidence of pediatric pleural empyema (complicated pneumonia) is increasing throughout the developed world, likely owing to pneumococcal serotype replacement and/or increasing antibiotic resistance.[3-12] Treatment options include conservative therapy with antibiotics alone or a variety of procedural interventions aimed at draining the pleural cavity including thoracentesis, chest tube placement, chest tube placement with intrapleural fibrinolytic therapy (CTWF), video-assisted thoracoscopic surgery (VATS), or open decortication. Pleural empyema is associated with important short-term effects including pain, dyspnea, and prolonged hospitalization. There has been a trend toward early, aggressive treatment in children with pleural empyema, in particular with either CTWF or VATS, reinforced by clinical guidelines[13-16] because this approach has been shown to improve short-term outcomes such as hospital stay, the need for further procedural intervention(s), and/or hospital use. However, little is known about the long-term outcomes of this condition including disruptions to parental work and child school life, radiologic outcomes, lung function, and quality of life, particularly in the era of CTWF and VATS. Such comprehensive data are important in informing clinicians, patients, and their parents contem-

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plating competing strategies for managing pleural empyema. The objectives of this study were to describe the outcomes of complicated pneumonia at a single center in terms of symptoms, signs, child and parental impact (missed school/parental work), radiographs, spirometry, and health-related quality of life (HR-QOL).

METHODS

SETTING AND PARTICIPANTS

This was a single-center prospective observational study of outcomes of childhood pleural empyema conducted at a large tertiary care children's hospital (The Hospital for Sick Children, Toronto, Ontario, Canada) recruited during 2 years (October 2008-October 2010) and followed up longitudinally for 1 year (last follow-up was in October 2011). All children (aged 0-18 years) admitted to the general pediatric or respiratory medicine wards or the intensive care unit with pleural empyema (complicated pneumonia), defined as ultrasound evidence of loculations and/or septations or frank pus obtained on thoracentesis, were invited to participate regardless of therapy instituted (ie, antibiotic therapy alone, chest tube insertion, or VATS). Excluded were all children referred to our institution for a complication or therapeutic failure from a prior drainage procedure, as well as those with simple (nonloculated) parapneumonic effusions, malignant effusions, chronic lung disease, cystic fibrosis, immunodeficiency, or tuberculosis. The study protocol was approved by the hospital's institutional review board. Informed consent, and, when applicable, assent were obtained from all participants.

Inpatient management and discharge of the patients was left to the discretion of the staff physicians who attended these wards. At the time of the study, there was no local clinical practice guideline for managing pleural empyema, although at our institution, most children treated with a drainage procedure receive an image-guided small-bore (10 French) pigtail catheter insertion, usually with instillation of fibrinolytics (tissue plasminogen activator).[17]

MEASURES

Inpatient

At baseline, data were collected on child age, sex, comorbidities (eg, asthma), and a variety of clinical admission parameters (ie, respiratory rate, antimicrobial use prior to hospitalization, days of fever, white blood cell count, and effusion characteristics and size). Diagnostic imaging was reviewed by a single radiologist (J.T.), blinded to the clinical history, who further categorized the effusion characteristics based on ultrasound (multiseptated and/or presence of debris) and the effusion size based on chest radiography. To account for age-dependent differences in sizing, radiographs were measured as the proportion of the hemithorax estimated to be occupied by the parapneumonic effusion. For children transferred from community hospitals, efforts were made to obtain clinical data from the referring institution. We collected data on interventions in hospital, including drainage procedures (eg, chest drain with or without fibrinolytics or VATS), and medical therapies (eg, antibiotic use). Readmission data were collected from hospital databases and potential readmissions to other hospitals were ascertained from parents.

Outpatient

At discharge from the hospital, parents of recruited children were given diaries to record symptoms (eg, cough, fever), days of child school loss, and days of parental work loss. Follow-up was arranged for 1 month, 6 months, and 12 months postdischarge. At follow-up visits, all patients were examined by a minimum of 2 study clinicians, and discrepancies were resolved by consensus.

SYMPTOMS/SIGNS AND CHILD/PARENT IMPACT

Parents were asked to record in the diary at least once a week for the first month and then once a month thereafter. They were instructed to measure the child's temperature if fever was suspected. To account for different parental methods of measuring fever, we defined a fever as a record of 38°C or greater on a home thermometer. Persistent cough was defined as a cough described as happening for at least 50% of diary recordings (≥2 of 4 weeks in first month and ≥3 months in subsequent follow-ups).[18] Child school loss was only reported for those children who were school aged and summer holidays were excluded. Parental work loss was only reported among parents who were employed. Diaries were reviewed at clinic visits together with the study research coordinator. At each clinic visit, patients were examined and weighed. Tachypnea was defined using the World Health Organization age-specific criteria (>50 breaths/min for 2-12 months, >40 breaths/min for 1-5 years, and >20 breaths/min for ≥5 years).[18] Failure to thrive was defined as weight below the third percentile or weight that crosses 2 centiles on standard World Health Organization growth curves (http://www.cdc.gov/growthcharts/who_charts.htm).

RADIOGRAPHS

A chest x-ray was performed at 1 month in accordance with clinical guidelines.[13] To minimize radiation exposure, repeat x-rays were only performed at subsequent visits if abnormalities persisted. Given that pleural thickening is of undetermined clinical significance, repeat radiographs were not performed for this indication alone. Follow-up radiographs were reviewed by the study radiologist (J.T.) blinded to their clinical report using the same scoring system used in the baseline x-rays. To ensure reliability, comparisons were made of all radiographs that were evaluated as normal with their clinical report; no discrepancies were found.

SPIROMETRY

Spirometry was performed according to international standards[19] using pediatric reference equations[20] to calculate the percentage of predicted values for age, height, and sex on all patients who were able to provide reliable results (generally aged ≥5 years). All spirometry results were interpreted by the study pulmonologist (S.D.), blinded to clinical details. Spirometry results were categorized as normal if forced expiratory volume in 1 second, forced vital capacity, and forced expiratory volume in 1 second/forced vital capacity were all greater than 80% predicted. Abnormalities were categorized by type (ie, obstructive, restrictive, or mixed) according to standardized interpretative strategies.[21] Severity of spirometric abnormality was classified based on the forced expiratory volume in 1 second, according to reference standards (ie, mild >70%, moderate 50-69%, and severe <50% predicted).[21]

HR-QOL

At all follow-up visits for children aged 2 years or older, parental proxies were asked to complete a standardized 23-item generic HR-QOL questionnaire, the Pediatric Quality of Life Inventory (PedsQL). Children aged 5 years or older were asked to fill the child self-report PedsQL.

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ANALYSIS

Descriptive statistics (means [SD] or medians [range] or proportions) were used to describe findings at baseline and at each of the follow-up visits. Given the objective to describe long-term outcomes (ie, at 12 months), we analyzed missing data using the principle of last observation carried forward. For instance, if patients did not attend a 12-month follow-up visit, data at 6 months were used as their long-term outcome. An abnormal PedsQL score was also designated as a last observation score that was at least 1 standard deviation below the mean from population normative data for healthy children.[22] Comparisons were also made between subjects and normative data for the PedsQL with a population of children with a common chronic respiratory disease (ie, asthma),[22] using independent *t* tests. All analyses were conducted on Minitab 14 (Minitab).

RESULTS

PATIENT CHARACTERISTICS

Eighty-four of a total of 88 eligible patients (95%) were recruited, of whom 2 (2%) chose not to attend any follow-up appointments owing to geographic distance, thus they were excluded from the 82 patients included in the analysis (**Table 1**). Attendance at follow-up visits included 82 patients (100%) at 1 month, 74 (90%) at 6 months, and 59 (72%) at 12 months. Most children in the cohort were managed with a chest drain (51 [62%]), of which 40 (79%) were instilled with fibrinolytics. No patients were treated with VATS, and no patients required any secondary (salvage) surgical procedures during the initial hospitalization. Eight patients (10%) were admitted to the pediatric intensive care unit (PICU); all of these patients were managed with a chest drain. There were no deaths. All patients received parenteral antibiotics, and 74 (90%) received multiple antibiotics.

READMISSIONS

A total of 6 patients (7%) were readmitted for reasons related to empyema, all within the first month posthospitalization. All 6 were readmitted for respiratory symptoms and/or ongoing fever. In their initial hospitalization, 2 (33%) had been admitted to the PICU, and 5 (83%) had been treated with a chest drain. Three patients presented with a pneumothorax and 3 with a persistent pleural effusion. Three patients required a procedural intervention during the readmission; 2 with a reinsertion of a chest drain for a pneumothorax, and 1 previously treated with antibiotics alone had a chest drain inserted for the first time for fluid accumulation.

SYMPTOMS/SIGNS AND CHILD/PARENT IMPACT

Ongoing symptoms such as fever and cough were common in the first month following hospital discharge but then declined in frequency (**Table 2**). Failure to thrive was documented in 2 patients (2%) in the first month, both of whom had been of normal weight at the time of admission to hospital. Both children were of normal weight on subsequent follow-up. Most school-aged children (59%) missed school in the first month and 29% of parents reported work loss, but both the proportion of those with school and/or work loss and the amount of time missed declined during the follow-up periods.

Table 1. Cohort Characteristics

	No. (%)
Demographics	
Age, median (IQR), y	3.6 (2.3-5.6)
Male	45 (55)
Race/ethnicity	
White	30 (37)
Asian or Pacific Islander	24 (29)
African Canadian	4 (5)
Hispanic	2 (2)
Other	15 (18)
Preferred not to answer	7 (8)
History of asthma	6 (7)
Referred from community hospital	58 (71)
Presenting features at admission	
History of fever	69 (84)
Tachypnea[a]	57 (70)
Duration of fever, mean (SD), d	7.8 (5.3)
White blood cell count, mean (SD), $\times 10^9$/L	19.6 (8.2)
Ultrasound findings	
Multiseptated	70 (85)
Debris	63 (77)
Unclear, poor quality of imaging	2 (2)
Estimated pleural effusion size, x-ray	
Fluid blunting of costophrenic angle but <25% of hemithorax	18 (22)
Fluid occupying 25-50% of hemithorax	20 (24)
Fluid occupying 50-75% of hemithorax	16 (20)
Fluid occupying >75% of hemithorax	22 (27)
Unclear	6 (7)
Hospital therapy	
Parenteral antibiotics	82 (100)
Multiple parenteral antibiotics	74 (90)
Vancomycin	46 (56)
Chest drain	51 (62)
Chest drain and fibrinolytics, n/N (%)	40/51 (78)
Positive cultures, blood and/or pleural	22 (27)[b]
Positive blood culture	13 (16)
Hospital outcomes	
LOS in tertiary care hospital, median (IQR), d	10 (6-14)
Total LOS, community and tertiary care hospitals, median (IQR), d	12 (8-18)
PICU admission	8 (10)

Abbreviations: IQR, interquartile range; LOS, length of stay; PICU, pediatric intensive care unit.

[a] Based on first vital signs recorded in hospital; defined using the World Health Organization age-specific criteria (>50 breaths/min for 2-12 mo, >40 breaths/min for 1-5 y, and >20 breaths/min for ≥5 y).[18]

[b] Sixteen patients (73%) tested positive for *Streptococcus pneumoniae*, 2 (9%) for *Streptococcus pyogenes*, 1 (5%) for *Staphylococcus aureus* (methicillin sensitive), 1 (5%) for *Staphylococcal aureus* (methicillin resistant), and 2 (9%) for other (*Actinomyces naeslundii* and *Fusobacterium*).

SPIROMETRY AND RADIOGRAPHS

At 1 month, abnormal spirometry results were noted in 7 of 20 patients (35%) who were able to complete the testing, of which 4 were mild restrictive, 2 were mild obstructive, and 1 was mild mixed (**Figure 1**). Abnormal radiographs were noted at 1 month in 24 of 82 patients

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Table 2. Symptoms/Signs and Child/Parent Impact

	No. (%)			
	1-Mo Follow-up, 1 Mo of Data (n = 82)	6-Mo Follow-up, 5 Mo of Data (n = 74)	12-Mo Follow-up, 6 Mo of Data (n = 59)	Last Observation (n = 82)
Symptoms/signs				
Diarized				
Fever, temperature ≥38°C measured at least once	18 (22)	13 (18)	11 (19)	12 (15)
Cough, ≥2 wk in first follow-up and ≥3 mo in subsequent follow-up	28 (34)	19 (26)	2 (3)	2 (2)
Exertional dyspnea	8 (10)	4 (5)	0 (0)	2 (2)
Chest pain	2 (2)	3 (4)	2 (3)	3 (4)
At clinic visit				
Fever, temperature ≥38°C tympanic	0 (0)	0 (0)	2 (3)	2 (2)
Failure to thrive, weight ≤3% for age or crossing 2 centiles	2 (2)	0 (0)	0 (0)	0 (0)
Tachypnea[a]	0 (0)	0 (0)	0 (0)	0 (0)
Abnormal breath sounds	21 (26)	1 (2)	1 (2)	3 (4)
Child/parent impact				
Children who missed school, n/N (%)[b]	10/17 (59)	8/20 (40)	6/17 (35)	9/20 (45)
Child school loss, median (IQR), d	5 (4-9)	2 (2-2)	2.5 (1-7)	2 (2-3)
Parents who missed work	19 (23)	7 (9)	2 (3)	4 (5)
Work loss for parents, median (IQR), d	5 (3-11)	2 (1-3)	8.5 (2-15)	8.5 (2-20)

Abbreviation: IQR, interquartile range.
[a] Defined using the World Health Organization age-specific criteria (>50 breaths/min for 2-12 mo, >40 breaths/min for 1-5 y, and >20 breaths/min for ≥5 y).[18]
[b] Among school-aged children, excluding those in the first month who were discharged from hospital during summer breaks.

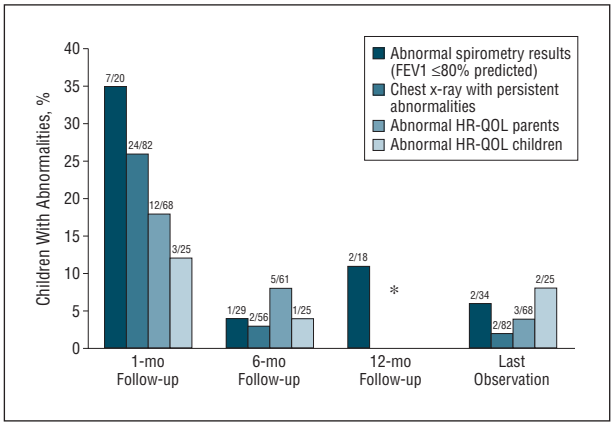

Figure 1. Abnormal radiography (excluding pleural thickening), spirometry, and health-related quality of life (HR-QOL) data. Health-related quality of life was defined as an abnormal Pediatric Quality of Life Inventory score if the child or parental proxy report total score was at least 1 standard deviation below the mean from population normative data for healthy children.[22]
* indicates no abnormalities in any x-rays (n = 13) or in parent (n = 61) or child (n = 25) scoring of the Pediatric Quality of Life Inventory.
FEV1 indicates forced expiratory volume in 1 second.

(29%). Twenty-two patients (27%) had pleural effusions, 3 (4%) had pneumatoceles, and 2 (2%) had pleural abscesses. Two of the 3 pneumatoceles were present in the 6-month radiographs, but they all completely resolved by 12 months. Both spirometric and radiographic assessments improved from first to last follow-up, and more children were able to complete reliable spirometric assessments over time (Figure 1). In the last follow-up, 2 of 34 patients (6%) had abnormal spirometry results, both with mild obstructive lung disease. Neither of these children had a history of asthma or previous (pre-empyema) spirometry performed. Abnormal radiographs were reported in 2 of 82 patients (2%) at last follow-up. Pleural thickening was found in 70 of 82 patients (85%) and measured a mean (SD) of 1.5 (1) mm. Among the subgroup of 8 patients admitted to the PICU, abnormal spirometry results at 1 month were noted in 4 of 8 patients (50%) at 1 month and 1 of 8 patients (12%) at 12 months; 2 of 8 patients (25%) had radiographic abnormalities at 1 month that normalized at 12 months.

Of the 4 cases with persistent spirometric or radiographic abnormalities, 1 was treated with a chest tube with fibrinolytics, 1 was treated with a chest tube alone, and 2 were treated with antibiotics alone. Two patients (aged 12.3 years and 5.7 years) had spirometric abnormalities, both with mild obstructive lung disease; 1 of these patients had 1.5-mm pleural thickening but otherwise neither had any radiographic abnormalities. Two patients had small residual pleural effusions. One of these patients (aged 3.2 years) had this noted at 1 month and was too young to undergo spirometry reliably; the patient did not return for any further follow-up. The other patient (aged 6.7 years) had a residual effusion at 6 months that was asymptomatic and improved from the 1-month radiograph. His spirometry results were normal and the patient did not return for any further follow-up. All 4 patients with abnormal spirometry results and/or radiographs at the last observation were asymptomatic at the time.

PedsQL

Pediatric Quality of Life Inventory data were available for 70 parents (85%) and 32 children (39%), and they improved from first to last follow-up (Figure 1). By the last follow-up, abnormal PedsQL scores were noted by 3 of 68 parents (4%) and 2 of 25 children (8%). Overall, HR-QOL was rated as higher in the empyema study cohort than for children with asthma by both the parental proxies and the children themselves ($P < .001$ for total scores and for physical, emotional, social, and school do-

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mains) (**Figure 2**). All 4 patients with persistent spirometric or radiographic abnormalities had normal PedsQL scores at that time (parent reported [n = 4], child reported [n = 2]).

COMMENT

The results of our study demonstrate that although a large proportion of children continued to exhibit signs and symptoms of pleural empyema in the month following discharge from hospital, in most cases, resolution occurred within 12 months. Signs and symptoms decreased, radiographs improved, spirometry results normalized, and both parental and child perceptions of HR-QOL were similar to healthy children. By the last observation, less than 6% had abnormal spirometry or abnormal radiography results, and those who did had mild abnormalities reported, with normal results in all other outcomes assessed. These findings support the view that empyema in children is a condition with substantial short-term morbidity but little long-term sequelae.

Despite inclusion criteria that were very similar to those of clinical trials and practice guidelines that recommend drainage procedures (eg, 71% of the overall group had >25% of the hemithorax involved, 85% had multiple septations on ultrasound, and the group had on average more than a week of fever at presentation), more than a third of the patients in this cohort were not treated with any drainage procedure, and only 2 patients received a second drainage procedure (a chest tube reinsertion); no salvage surgical procedures were performed. This suggests that for those children without substantial respiratory compromise or for those with prolonged recovery following initial drainage, the treatment of pleural empyema can be thought of as a preference-sensitive condition where an improvement in short-term outcomes (eg, length of stay) conferred by an interventional approach is weighed against the excellent long-term outcomes that may be independent of the treatment approach during the acute phase of the illness.

To our knowledge, this study is the largest to focus on long-term outcomes in pediatric empyema and the first to comprehensively describe the outcomes of childhood empyema with serial measurements. A librarian-assisted compilation of the existing literature on patient outcomes is summarized in the eTable (http://www.archpediatrics.com). Among the 5 contemporary studies published in the last 20 years during which the epidemiology and treatment of empyema has changed, findings are conflicting. Kohn et al[23] described persistent symptoms such as exertional dyspnea and abnormal lung function (either restrictive or obstructive lung disease) in more than a third of patients, while 4 other studies described that almost all patients in follow-up had normal lung function,[24] signs,[25] symptoms,[26] and radiographs.[24-27] Our results seem to support the idea that mild residual radiographic abnormalities such as pleural thickening are common, long-lasting, and of likely minimal clinical importance in pediatric empyema. Furthermore, substantial radiographic and spirometric abnormalities were common at 1 month. Some guidelines recommend radiographs be performed 4 to 6 weeks post-hospitalization to ensure resolution.[13,28] Our findings suggest that delaying repeat radiographs until at least 6 to 12 months may be more warranted in patients without any residual signs or symptoms to avoid unnecessary repeat imaging.

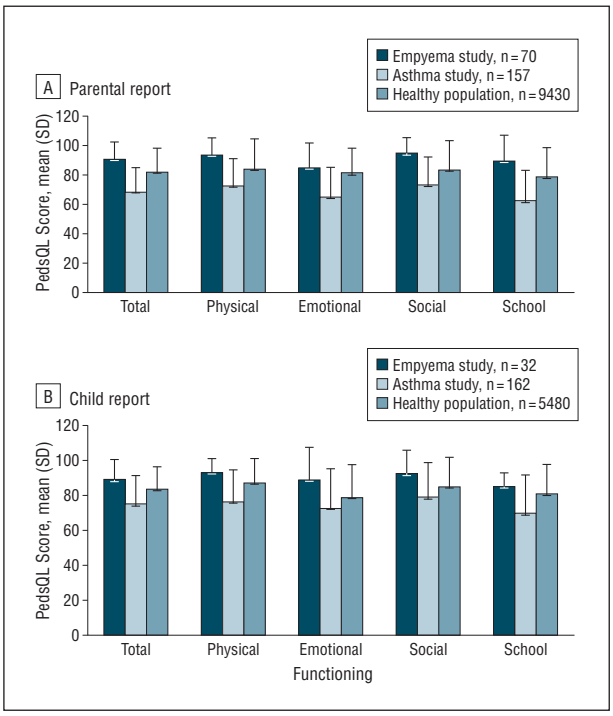

Figure 2. Parent-completed (A) and child-completed (B) Pediatric Quality of Life Inventory (PedsQL) scores for the empyema cohort at last observation compared with healthy control subjects[22] for summary score (total) and scale scores (physical, emotional, social, and school functioning). Overall scores for the empyema cohort were higher than for children with asthma in all domains ($P < .001$) in both parents and children. Correlation between overall scores for parent-child dyads (n = 32) was $r = 0.237$. The error bars indicate standard deviations.

There are a number of important limitations to our study. We conducted our study at a single center. We tried to include patients with similar features to those used in clinical trials of interventions in childhood pleural empyema. Nevertheless, generalizability to other settings where therapies may differ, such as those that use VATS as primary therapy, is limited. Our sample size was limited, thus we were unable to make inferences about differences between subgroups of patients (eg, those admitted to the PICU or those with readmissions). Although we tried to collect comprehensive outcomes, given the young age of the cohort, we were unable to obtain reliable spirometry results or HR-QOL data on many or conduct more comprehensive functional testing (eg, exercise testing). There were some withdrawals, which we tried to account for using a conservative reporting strategy focusing on the last observation before loss to follow-up. Lastly, although those children who were not drained had excellent outcomes, this could be because they were not as sick on presentation (eg, none were admitted to the PICU).

In conclusion, clinically important phenomena persist in the short-term after children are discharged from hospital with pleural empyema, but 1-year outcomes are excellent. This information may aid decision making for clinicians and families balancing the risks and benefits of various competing strategies for managing empyema.

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